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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,679	05/17/2007	Jo Klaveness	PN0397	7412

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EXAMINER
SCHLIENTZ, LEAH H

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,679	KLAVENESS ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/5/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 7/23/2009, in reply to the Office Action mailed 6/24/2009, is acknowledged and has been entered. Claims 1-4, 6-8 and 11 have been amended. Claims 5, 9, 10, 12 and 13 have been cancelled. Claims 1-4, 6-8 and 11 are pending and are examined herein on the merits for patentability.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 3/5/2009 was filed after the mailing date of the Office Action on 12/9/2008. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

Any rejection or objection not reiterated herein has been withdrawn as being overcome by amendment.

Applicant's arguments have been fully considered but are moot in view of new grounds for rejection set forth hereinbelow, necessitated by amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of optical imaging of oesophageal cancer or Barrett's oesophagus involving administering a contrast agent with an affinity for an abnormally expressed biological target associated with oesophageal cancer or Barrett's oesophagus, wherein the biological target is selected from E-cadherin, CD44, P62/c-myc (HGF receptor), p53 and EGFR/erB-2. Dependent claims recite a contrast agent of formula I, V-L-R, wherein V is one or more vector moieties having affinity for an abnormally expressed target in oesophageal cancer or Barrett's oesophagus, L is a linker moiety or a bond and R is one or more reporter moieties detectable in in vivo optical imaging. In dependent claims the contrast agent has a molecular weight below 14000 Daltons. However, the claims are devoid of any structural elements that correlate to the function which is to be achieved with the claimed composition. For example, a vast number of potential "vector moieties having an affinity for an abnormally expressed target in oesophagael cancer or Barrett's oesophagus" may be found in the art to be

capable of having the claimed function. Applicant has identified in the instant specification a diverse variety of targets for which the vector may have affinity including E-cadherin, CD44, P62/c-myc (HGF receptor), p53 or EGFR/erB-2, etc. among others (see paragraphs 0026-0048 of the instant specification). Such targets are widely varying in structure and would have an almost unlimited number of potential vectors which may have affinity thereto. The vectors themselves may be almost unlimited including various peptide sequences, small molecules, antibodies, nucleic acid sequences, etc. It is clear that Applicant had possession of such a few specific formulations at the time of filing using specific and defined vectors as identified in paragraphs 0061-0066 and the Examples, but the specification as originally filed does not provide support that Applicant had possession of the invention as generically claimed by function alone in the instant claims. For example, to arrive at the claimed contrast agent, one would have to determine the type of vector having affinity to which out of an extremely large number of targets to conjugate to which out of an almost unlimited number of potential optical imaging moieties to be combined into a single agent, and further which out of an almost unlimited number of potential functional groups or chemical reactions would be necessary to derivatize and conjugate the moieties into a single agent having the claimed functional properties. One would have to select which portions of which molecules would be suitable to be conjugated to the others and on what positions of the molecules with various substituents. Applicant's limited disclosure of a particular compound which has the claimed functional properties does not provide support that Applicant envisaged the

invention as a whole which is broadly claimed solely by function. In the instant case, a definition by function alone does not appear to sufficiently describe the claimed invention because it is only an indication of what the agent does, rather than what it is. See MPEP 2163 and *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406.

Applicant argues on page 5 of the Response that claim 1 has been amended to include the elements of previous claims 10 and 5, and is no longer to optical imaging contrast agents *per se*. Hence, it can no longer be argued that the claim pertains to compounds defined only by their function. In addition, the claim scope has been limited to the five biological targets of previous claim 5. Applicants contend that the specification provides sufficient information for the person skilled in the art to reproduce the method of amended claim, and that the person skilled in the art can either use the contrast agents described in the specification, or generate new ones. Applicants suggest that the claim scope for such an optical imaging method claim should not be limited by the possible future advent of new targeting molecules. If a person skilled in the art has available a compound with affinity for E-cadherin, CD44, P62/c-myc (HGF receptor), p53 or EGFR/erB-2, then labelling such a compound with an optical reporter is taught by the present specification.

This is not found to be persuasive. In order to practice the claimed method, one would necessarily be in possession of the contrast agent, thus a reasonable description of the contrast agent which are used to practice the method is necessary. While Applicant has provided a description of a few

specific vectors (i.e. a single peptide sequence which binds p53 (paragraph 0061), a 4-anilinquinazoline compound which targets EGFR/erB-2 (paragraph 0062). Such a limited disclosure of a single vector for each of the claimed receptors which are associated with esophageal cancer or Barrett's esophagus does not provide sufficient description to show that Applicant was in possession of the full scope of a contrast agent comprising an optical imaging moiety and any vectors (e.g. any small molecule, any peptide, any oligonucleotide, any antibody etc) which may target the claimed receptors. With regard to Applicant's argument that the claim scope should not be limited by the possible future advent of new targeting molecules, and that if a person skilled in the art has available a compound with affinity for one of the targets described, then labeling such a compound with an optical reporter is taught by the specification, this is not found to be persuasive because the specification has not provided a clear description of the full scope of targeting vectors which were envisaged at the time the specification was filed. Future-developed targeting moieties would not be encompassed by vectors that Applicant was in possession of at the time the application was filed, especially since Applicant has only described a single vector for each target/receptor. In the instant case, a definition by function alone does not appear to sufficiently describe the claimed invention because it is only an indication of what the agent does, rather than what it is. See MPEP 2163 and *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. The claims are more broad than the enabling disclosure. For example, with regard to the vector moiety the

claims identify the moiety by what it does (i.e. targets p53, for example), rather than what it is (i.e. a structurally defined peptide sequence such as Cys-Gly-Pro-Leu-Gly-Leu-Leu-Ala-Arg-OH).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

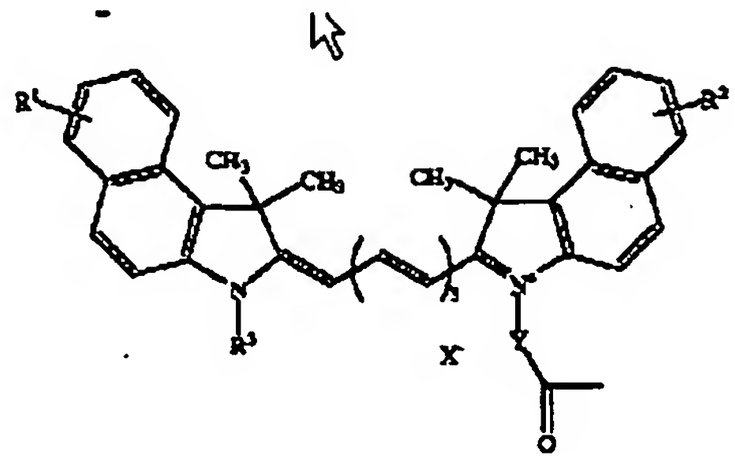
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 7, 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al. (US 5,968,479) in view of Iversen (US 6,365,577).

Ito discloses a diagnostic marker containing (a) a detection system such as an antibody and (b) a fluorescent functional group that is bound to the detection system and represented by the formula:



The diagnostic marker emits fluorescence having a wavelength of 780 nm or more when irradiated with near or far infrared rays, and thus useful for infrared endoscopic diagnosis or identification of a focus in surgical operation (abstract). As pharmacologically and pharmaceutically acceptable additives for the manufacture of the diagnostic agent of the present invention, for example, excipients, disintegrators, etc. (column 11, lines 23+). Targeting to p53 protein for *in vitro* and *in vivo* targeting of cancer of the stomach is disclosed (column 9, lines 10-30).

Ito does not specifically recite imaging esophageal cancer via p53 targeting.

Iversen discloses that preferred target cells are cancer cells characterized by p53 expression. Such cancers include those of bladder, brain, breast, cervix, colon, esophagus, larynx, liver, lung, ovary, pancrease, prostate, skin, stomach and thyroid.

It would have been obvious to one of ordinary skill in the art at the time of the invention to perform optical imaging of esophageal cancer upon administration of the p53 antibody-fluorescent compound conjugates disclosed by Ito. While Ito does not specifically recite that esophageal cancer is imaged

with his compositions, i is known in the art that p53 is overexpressed in both esophageal cancer, as well as stomach cancer, as shown by Iversen. It would have been further obvious to image/diagnose esophageal cancer in order to expand upon the cancer types for which the conjugates of Ito are useful. One would have had a reasonable expectation of success in doing so because Iversen teaches the correlation between erbB-2 and esophageal cancer.

Claims 1-4, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quinn *et al.* (US 7,585,509) in view of Chiang *et al.* (*Clin. Cancer Res.*, 1999, 5, p. 1381-1386).

Quinn discloses a method for targeting an agent to a **cancer cell expressing ErbB-2** comprising bringing said cancer cell into contact with a peptide-agent complex, wherein said peptide comprises the sequence KCCYSL (SEQ ID NO:1) and said peptide binds to the extracellular domain of ErbB-2, wherein said agent is a **diagnostic agent**, a chemotherapeutic, a radiotherapeutic, a toxin or a cytokine (claim 1). The diagnostic agent may be a **fluorescent label** (claim 3). The complex further comprises a linking moiety that connects said agent and said peptide (claim 13). There are provided methods for diagnosing ErbB-2-positive cancer in a subject comprising (a) administering to the subject a peptide-diagnostic agent complex, wherein the peptide comprises the sequence KCCYSL; and (b) assessing the amount and/or localization in the subject, of the diagnostic agent. The diagnostic agent may be a radiolabel, a chemilluminescent label, a fluorescent label, a magnetic spin

resonance label, or a dye. The patient may or may not have been previously diagnosed with cancer. The patient may have previously received a cancer therapy, or may be concurrently receiving a cancer therapy. The may be patient at an elevated risk for cancer. The assessing may comprise organ or whole body imaging, and may further comprise excising a tumor localized by the diagnostic agent (column 2, lines 38+). **Fluorescent labels contemplated for use as conjugates** include Alexa 350, Alexa 430, AMCA, BODIPY 630/650, BODIPY 650/665, BODIPY-FL, BODIPY-R6G, BODIPY-TMR, BODIPY-TRX, Cascade Blue, Cy3, Cy5,6-FAM, Fluorescein, Isothiocyanate, HEX, 6-JOE, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, REG, Rhodamine Green, Rhodamine Red, Renographin, ROX, TAMRA, TET, Tetramethylrhodamine, and/or Texas Red (column 10, lines 42-50).

Quinn does not specifically teach that that esophageal cancer is imaged.

Chiang discloses that about 20% of esophageal adenocarcinomas show amplification of the *erbB*-2 oncogene, and that the capability to detect abnormalities in serum of esophageal cancer patients creates an opportunity to diagnose esophageal cancer and to monitor the outcome of treatment (page 1381).

It would have been obvious to one of ordinary skill in the art at the time of the invention to perform optical imaging of esophageal cancer upon administration of the erbB-2 receptor targeting peptide conjugates disclosed by Quinn. While Quinn does not specifically recite that esophageal cancer is imaged with his compositions, it is taught that erbB-2 is overexpressed in a

number of cancer types including those involving the female genital tract (e.g., endometrial cancer), gastric cancer and prostate cancer, and that a primary target for ErbB-2 targeted therapies is breast cancer, of which 20-30% show overexpression of this marker (column 30, lines 35+). It is known in the art that erbB-2 is also overexpressed in esophageal cancer, as shown by Chiang. Since Quinn generally teaches that his compositions are useful for diagnosing erbB-2-positive cancer in a subject (column 2, claim 1), and that erbB-2 is overexpressed in a number of cancer types, it would have been further obvious to image/diagnose esophageal cancer in order to expand upon the cancer types for which the conjugates of Quinn are useful. One would have had a reasonable expectation of success in doing so because Chiang teaches the correlation between erbB-2 and esophageal cancer.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory

period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS